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EXAMINER	
DUTT, ADITI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,737	CHAN ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 23 June 2009 has been entered in full. Claims 7, 10, 16-17, and 19-21 have been amended.

Election with traverse

2. Applicant's election with traverse of Group I, claims 1-16. 18, 21-23, in the reply filed on 23 June 2009 is acknowledged.

3. The traversal is on the ground(s) that in the absence of a serious search burden, the Examiner must examine all the claims on the merits even if the claims are directed to independent or distinct inventions. Applicant amends claims directed to Groups II and III to depend from Group I, thereby establishing a unity of invention between the claims of the three groups. Applicant asserts that there will not be an undue burden to search the amended claims, therefore, requests consideration of the currently amended claims 1-23 for instant examination. Applicant further submits that in light of the elected method claims, claims 24-25 (although presently withdrawn) directed to a pharmaceutical composition would not cause undue search burden.

4. Applicant's arguments are fully considered, however, are found to be persuasive in part. In view of the current claim amendments, the claims originally directed to Groups II and III, now fall within the scope of inventive Group I.

Therefore, claims 1-23 will be considered for examination in the instant application.

5. Applicant's arguments directed to the consideration of claims 24-25, however, are not found to be persuasive, because as stated in the previous Office Action dated 23 December 2008, the method claims and claims 24-25 directed to a product do not relate to a single inventive concept, and lack the same or corresponding technical features for reasons stated on record in the last Office Action. Furthermore, although the restriction requirement is not mandatory, the claims in such application can be restricted on the basis of lack of unity of invention at the discretion of the examiner. See 37 CFR 1.499. It is to be noted that "special technical features" means those technical features that define a contribution over the prior art (See M.P.E.P. 1850), and the prior art teaches the product of claims 24 and 25. Berry et al. (US patent number 6562781, dated 13 May 2003) teach pharmaceutical compositions comprising a combination of heparin and antithrombin III for treating thrombosis and related disorders (col 1, para 2; col 10, para 55-58). Thus, the apparent "special technical features" of these claims cannot form the basis of unity of invention, The invention of Group I, claims 1-23 forms a single inventive concept, therefore, represent a patentably distinct invention.

6. Additionally it is noted that pursuant to 37 C.F.R. § 1.475 (a), Unity of invention before the International Searching Authority, an international and a national stage application shall relate to one invention only or to a group of

inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Groups I and IV do not possess special technical features as set forth above.

7. Applicant is however, reminded that, upon allowance, the product used in the claimed method will be rejoined to the examined Invention. However, until an elected method claim is found allowable, an otherwise proper restriction requirement between product claims and process claims should be maintained (*In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b), 1184 O.G. 86 March 26, 1996).

8. **The requirement is still deemed proper and is therefore made FINAL.**

9. Claims 24 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 June 2009.

10. Claims 1-23, drawn to a method of preventing or reducing neurological events in a subject comprising administration of glycosaminoglycan and a serpin, are being considered for examination in the instant application.

Oath/Declaration

11. The oath or declaration is defective because:

The filing date of PCT/CA04/01497 is entered as 8/12/03, while the Application data sheet has the date as 8/12/04. Since this is a 2004 PCT, the 2003 date on the declaration is wrong.

Appropriate correction is required.

Drawings

12. The instant drawings do not comply with 37 C.F.R. § 1.84(U)(1), which states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. Figures 4, 5, 8 and 9 of the instant application, for example, are presented on two separate graphs. The two graphs, which are labeled “Figure 4”, "Figure 5”, “Figure 8” and “Figure 9” in the instant specification should be renumbered as “Figures 4A and 4B”, and so on. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly.

Specification

13. The disclosure is objected to because of the following informalities:

(i) The disclosure refers to Fig. 5 graphs as (5A) and (5B) on page 3, line 39. However, the drawings for figure 5 are not labeled as 5A and 5B.

(ii)The brief description does not describe the lower graph of Figure 4.

(iii) The description for Figures 8 and 9 in the disclosure, stating "during CPB and thereafter in the pig model" is unclear (page 4, lines 6-8). Are the 2 graphs in each of Figures 8 and 9 representing different models?

Appropriate clarification and correction are required.

Claim Objections

14. Claim 9 is objected to because of the following informalities:

Claim 9 recites the acronym "ATH". The acronym should be spelled out for clarity.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 4-6, 10-14,16-18 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claims 4-6 are rejected for being multiple dependent claims. Claims 4 and 6 each depend in part from claim 3, which itself is multiple-dependent. Claim 5 depends from 4 and therefore, has the same problems (depends from an improper multiple dependent claim).

17. Claim 18 is unclear and vague for reciting the limitation “preventing or reducing emboli from a bypassed heart region prior to removal of the region from bypass". It is not discernible as to what region is being removed and why is a heart region being removed? It is not clear whether the patients referred to in the claim have had part of their heart removed or not. On the one hand, the claim recites “…prior to the removal of the region from bypass”, which implies that either the region is removed, or alternatively that it is no longer being bypassed. However, the plain meaning of the term "bypass" is that blood flow is changed so that it no longer flows around a damaged coronary artery,. Therefore one of skill in the art could not determine which patients are included within claim 18, and whether a part of the heart of the patients is removed, or whether the blood is flowing through the damaged region or not. Appropriate clarification is required.

18. Claim 10 is indefinite for reciting “a procedure that **may** give rise to a neurological event" (emphasis added). In other words the limitation is interpreted as reading on a procedure that **may or may not** give rise to a neurological event.

The claim is speculative and fails to identify the metes and bounds of the related subject matter and how that could be ascertained in the stated invention.

It is noted that for the purpose of instant examination claim 10 is interpreted as reading on a procedure that could give rise to a neurological event.

19. Claims 11-14, 17, and 21-23 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing a neurological event associated with emboli or thromboemboli, wherein said event is caused by a surgical procedure affecting brain or cerebral circulation, comprising administration of therapeutically effective doses of heparin and antithrombin III, does not reasonably provide enablement for preventing or reducing any neurological event with or without a procedure, by administration of any glycosaminoglycan (GAG) and any serpin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these

claims. It is noted that the limitations “a glycosaminoglycan” and “a serpin” are interpreted as "any" glycosaminoglycan or serpin.

21. The claims are directed to a method of preventing or reducing neurological events associated with emboli or thromboemboli, in a subject comprising administration of a glycosaminoglycan (GAG) (heparin or low molecular weight heparin) and a serpin (antithrombin III or transgenic antithrombin III) (claims 1-6) prior to during or after a procedure that affects cerebral circulation (10-12, 15-16, 18); wherein heparin and antithrombin III (ATIII) form a covalently linked complex or conjugate ATH (claims 7-9); wherein the procedure is a surgical procedure (claims 13-14, 17). The claims also recite a method for reducing or preventing cerebral embolization by administering a pharmaceutical composition comprising the antithrombin III (ATIII) and heparin conjugate (claims 19-23).

22. With respect to claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1]), which states that claims must be given their broadest reasonable interpretation.

23. “During patent examination, the pending claims must be “given *>their< broadest reasonable interpretation consistent with the specification.” *In re Hyatt,* 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always

has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly that is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)".

24. As such, the broadest reasonable interpretation of claimed invention is drawn to a method for reducing or preventing any neurological event irrespective of a procedure by administration of any glycosaminoglycan and any serpin to a subject.

25. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

26. The specification of the instant application teaches that neurological events like stroke result from the generation of emboli or particulate matter in the brain or cerebral circulation during cardiac surgery (page 2, para 2; page 9, para 3), and further teach that GAG and serpin provide synergistic activity in preventing or reducing such events (page 3, para 1). The specification defines a neurological event as "an injury of the central nervous system following a medical procedure associated with embolization or embolism in the cerebral circulation".

Additionally, a neurological event can include neurocognitive and behavioral deficits (page 9, para 5). The specification also teaches that serpin is a serine protease inhibitor such as ATIII and heparin cofactor II, and further include derivatives, variants and analogs having similar structure or biological activity (page 4, lines 23-33). The specification further teaches that GAGs are mucopolysaccharides, that include heparin, chondroitin sulfate, keratan sulfate, chondroitin, gum Arabic, etc. (page 5, para 1). Furthermore, the specification discloses that ATH is a covalent complex between antithrombin (AT) and heparin (H), wherein AT is in the active conformation to bind and inactivate thrombin, thus preventing or reducing clot formation by having a rapid onset of action (page 6, para 1). Using a pig cardiopulmonary bypass (CPB) model (or a thrombosis model), the specification demonstrates that ATH administered during CPB result in fewer thrombi in the brain than that seen in animals given heparin alone (page 21, para 3; Figures 10, 11; page 23, Table 2). However, the specification does not provide any evidence or sound scientific reasoning that the limited information presented in the disclosure can be directly extrapolated to preventing or reducing any neurological event with or without the associated embolism, by administration of a pharmaceutical composition comprising any GAG and any serpin, wherein the event can be precipitated in the presence or absence of a surgical procedure. The specification also has not provided any working example or guidance regarding the prevention of a neurological event in a subject by the claimed method. It would require undue experimentation and making a

substantial inventive contribution for one skilled in the art to practice Applicant's invention, as currently claimed.

27. Relevant literature teaches a wide structural and functional diversity in GAG and serpin molecules and their receptors and ligands. Handel et al. (Ann Rev Biochem 74: 385-410, 2005) teach that GAGs such as heparin, chondroitins, etc. are highly diverse macromolecules that react with specific ligands and mediate specific physiological functions (page 387, Table 1). For example, heparan sulfate interacts with fibroblast growth factors to mediate tyrosine kinase signal transduction; heparin binds to AT for the inactivation of the coagulation cascade, prevention of thrombosis and related diseases, and so on (Handel et al. page 393, para 5; Berry et al. US Patent No. 6,562,781 B1, dated 13 May 2003; col 1, para 2). Silverman et al. (Methods 32: pages 71-72, 2004), teach that serpins constitute more than 1000 diverse sequences, of which many are orphans. Although serpins largely are serine proteinase inhibitors of the chymotrypsin, trypsin family, there are several serpins that belong to the non-inbibitor type. Furthermore, several serpin molecules including the cross-class serpins bind to a diverse array of biochemical molecules, proteinases, hormone binding proteins and ligands, mediating a wide range of functions such as chromatin condensation, etc. (Silverman et al., page 71, col 2, para 2; page 72, col 1, para 2). However, neither the instant disclosure nor the relevant art teaches that any GAG and/or serpin can be used for the prevention or reduction of any neurological event associated with any procedure.

28. Furthermore, the literature teaches that cardiac surgical procedures such as CPB result in stroke, cognitive dysfuction, seizures, etc. (Heyer et al. J Card Thor Vasc Anaes 16: 37-42, 2002; page 37, col 1, para 1-2). Heyer et al. further demonstrate that heparin bonded circuits reduce the number of emboli resulting from CPB, as well as the occurrence of cognitive dysfunction, when compared to the non-heparin bonded circuits (abstract; Figure 1). Ceustermans et al. (JBC 257: 3401-3408, 1982) teach that low molecular weight heparin has antithrombotic properties similar to high molecular weight heparin and is preferable because it causes less bleeding (page 3401, col 2, para 3). Also covalent complexes between heparin and ATIII are proven to have a better antithrombotic activity due to longer half life in circulation (page 3401, col 2, para 4). However, based upon the information and guidance available in the post/prior art literature, all GAGs cannot form covalent conjugates with any of the numerous variety of serpins, their analogs, variants or derivatives, and further have a specific functional activity of reducing any neurological event as broadly claimed. Furthermore, based upon the definition of a serpin in the instant specification, the genus can include all possible variants and derivatives (page 4, lines 23-33), with essentially any number of changes so that any biological activity is retained. No particular biological activity (for example, binding to a receptor or inducing a signaling cascade) is required, and the specification fails to show which regions of the serpin structures are either necessary or sufficient for the methods as claimed to work. Therefore, given the expansive definition of

what constitutes a serpin (which includes variants and derivatives), and the lack of guidance as to which regions of the disclosed serpin structure should be maintained in the variants, as well as the lack of working examples commensurate in scope with the very broad definition, undue experimentation would be required in order to make the full range of serpins, which are required as starting materials for the claimed methods. Knowing the large array of neurological events resulting with or without a surgical procedure, and further treating such complex events with the enormous number of combinations of GAGs and serpins would ensue numerous trial and error steps and a high degree of unpredictability of success. Undue experimentation will be required of a skilled artisan to make and use the invention as claimed.

29. Lastly, in making a determination of whether the application complies with the enablement requirement of 35 U.S.C. 112 first paragraph, each claimed invention must be evaluated to determine whether there is sufficient guidance provided and supported by working examples to inform a skilled artisan how to use the claimed invention without undue experimentation. Based on the broadest reasonable interpretation of the claimed invention, the term 'preventing' (recited in the claims) corresponds to total prevention or stopping of a neurological event. In the instant case, even though the claimed ATH conjugate is exemplified in the specification as reducing emboli or treating thromboemboli in the brain, there is no evidence that the reduction in emboli would necessarily and successfully prevent or stop the formation of emboli or any subsequent neurological event,

since there are multiple processes and factors that contribute to the development of neurological events, e.g. in case of cerebral injury and cognitive dysfunction due to cardiac surgery, various factors like the severity of aortic disease, length of CPB, etc. determine the formation of emboli (Heyer et al. page 40, col 2, para 2). The mere presentation of reduction of emboli in the brain in a pig model by administration of ATH during CPB, does not prove that ATH, or a combination of any GAG and any serpin will prevent a neurological event.

30. Due to the large quantity of experimentation necessary for reducing or preventing any neurological event with or without a procedure, by administration of any GAG and any serpin; the lack of direction/guidance presented in the specification; the complex nature of the invention; the state of the art teachings of several GAGs and numerous known and less known serpins, each having diverse functions and binding properties; and the breadth of the claims which fail to recite a specific procedure (e.g. cardiac surgery or CPB affecting cerebral circulation), a specific neurological event (e.g. associated with emboli), a specific GAG (e.g. heparin), and a specific serpin (e.g. ATIII); undue experimentation would be required of the skilled artisan to practice the instant invention, as currently claimed.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

31. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

32. The claims are directed to a method of preventing or reducing neurological events associated with emboli or thromboemboli, in a subject comprising administration of a glycosaminoglycan (GAG) (heparin or low molecular weight heparin) and a serpin (antithrombin III or transgenic antithrombin III) (claims 1-6) prior to during or after a procedure that affects cerebral circulation (10-12, 15-16, 18); wherein heparin and antithrombin III (ATIII) form a covalently linked complex or conjugate ATH (claims 7-9); wherein the procedure is a surgical procedure (claims 13-14, 17). The claims also recite a method for reducing or preventing cerebral embolization by administering a pharmaceutical composition comprising the antithrombin III (ATIII) and heparin conjugate (claims 19-23).

33. The specification of the instant application teaches that neurological events like stroke result from the generation of emboli or particulate matter in the brain or cerebral circulation during cardiac surgery (page 2, para 2; page 9, para 3), and further teach that GAG and serpin provide synergistic activity in preventing or reducing such events (page 3, para 1). The specification defines a neurological event as “an injury of the central nervous system following a medical procedure associated with embolization or embolism in the cerebral circulation”. Additionally, a neurological event can include neurocognitive and behavioral deficits (page 9, para 5). The specification also teaches that serpin is a serine

protease inhibitor such as ATIII and heparin cofactor II, and further include derivatives, variants and analogs having similar structure or biological activity (page 4, lines 23-33). The specification further teaches that GAGs are mucopolysaccharides, that include heparin, chondroitin sulfate, keratan sulfate, chondroitin, gum Arabic, etc. (page 5, para 1). Furthermore, the specification discloses that ATH is a covalent complex between antithrombin (AT) and heparin (H), wherein AT is in the active conformation to bind and inactivate thrombin, thus preventing or reducing clot formation by having a rapid onset of action (page 6, para 1). However, the brief description in the specification describing one example of ATIII as a serpin, does not teach functional, structural or binding characteristics of all encompassed serpins, for the claimed method of reduction or prevention of all neurological events. The brief description in the specification of one example of ATIII, and covalent complexes between ATIII and heparin (ATH), is not adequate written description of an entire genus of serpins and the entire genus of covalent complexes to promote the reduction or prevention of embolism or having antithrombotic activity.

34. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a

relationship between the structure, function, or properties of the claimed genus of innumerable serpins comprising variants, analogs and derivatives in the claimed method of preventing or reducing any neurological event. In this case, the only factor present in the claim is a recitation of preventing or reducing neurological events by administering ATIII and heparin, or covalent complexes of the same. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

35. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

36. With the exception of heparin, ATIII, ATH and a neurological event associated with thromboemboli in the cerebral circulation due to a surgical procedure like CPB, the skilled artisan cannot envision the detailed structure and functional properties of the encompassed serpins, covalent complexes, and all methods for using the genus of serpins to prevent and reduce a genus of neurological events, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the claimed

method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

37 One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

38. Therefore, only ATIII, ATH, a neurological event associated with thromboemboli, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

39. Claims 1-23 are rejected under 35 U.S.C. 102(a) and 102(e) as clearly anticipated by Berry et al. (US Patent No. 6,562,781 B1, dated 13 May 2003, filed 30 November 1995).

40. The claims are directed to a method of preventing or reducing neurological events associated with emboli or thromboemboli, in a subject comprising administration of a GAG (heparin) and a serpin (ATIII or transgenic ATIII) (claims 1-6) prior to during or after a procedure that affects cerebral circulation (10-12, 15-16, 18); wherein heparin and antithrombin III (ATIII) form a covalently linked complex or conjugate ATH (claims 7-9); wherein the procedure is a surgical procedure (claims 13-14, 17). The claims also recite a method for reducing or preventing cerebral embolization by administering a pharmaceutical composition comprising the antithrombin III (ATIII) and heparin conjugate (claims 19-23).

41. Berry et al. teach the therapeutic use of a covalent conjugate or complex between ATIII and heparin in mediating anticoagulative properties (col 2, para 4). The reference also teaches treating a large array of thrombotic and related diseases associated with surgical procedures like CPB (col 4, lines 49, 57-58), and further teach arresting the “development or progression of clinical symptoms” (col 4, lines 44-45) by administering the ATIII-heparin conjugate, thereby

inherently and implicitly encompassing symptoms that certainly "may give rise to a neurological event" (as recited in claim 10 for example). Furthermore, the reference teaches the administration of pharmaceutical compositions comprising these conjugates in therapeutically effective dosage in mammals such that the conjugate reduces or treats thrombotic states (col 9, lines 59-67; col 10, lines 55-58). Although the reference does not explicitly teach neurological events, it is well established and evidenced in relevant art that cardiac surgical procedures like CPB can lead to cerebral injury due to emboli formation, resulting in neurological events like stroke, seizures, etc. (Heyer et al. J Card Thor Vasc Anaes 16: 37-42, 2002; page 37, col 1, para 1-2). Additionally, the association of emboli or thromboemboli, and the subsequent generation of embolism is an accompanying consequence of CPB, the number of emboli being directly correlated to the length of the surgical procedure (Heyer et al. page 40, col 2, para 1). Still further, since the instant specification has not defined transgenic ATIII as a molecule that is structurally different from native ATIII, "transgenic ATIII" can be construed as a product-by-process limitation. Unless there is evidence otherwise, it would be reasonable to presume that transgenic ATIII is the same product as native ATIII, even though the former may be made by a different process. Please note that product-by-process claims are not limited to the manipulations of the method, only the structure that is implied therefor. The patentability of a product does not depend on its method of production. See M.P.E.P. 2113. Furthermore, please note that the present claims encompass preventing. This means that the scope

of the claims is administration to any patient, whether or not they have or are at risk of having "neurological events" or thrombi, etc. Because Berry et al. teach administering to a patient, the patent anticipates the present claims. Because the method steps taught by the reference are identical to the claimed invention, the reference anticipates the invention.

42. Claims 1-23 are rejected under 35 U.S.C. 102(e) as clearly anticipated by Berry et al. (US Patent No. 7,045,585 B2, filed 20 March 2002).

43. Berry et al. teach the therapeutic use of a covalent conjugate or complex between ATIII and heparin in treating or preventing thrombogenesis (abstract). The reference also teaches methods for preventing or treating excess thrombin generation due to vascular or heart surgical procedures resulting in cerebral vascular accidents large array of thrombotic and related diseases associated with surgical procedures like CPB (col 15, para 3). Furthermore, the reference teaches the administration of pharmaceutical compositions comprising these conjugates in therapeutically effective dosage in mammals such that the conjugate reduces or treats thrombotic states (col 22, para 2). It is to be noted that emboli is defined in the instant specification as a particulate matter composed of clotting factors like fibrin, platelets, etc. (page 9, para 3), i.e. essentially a clot that blocks vessels. Additionally, the association of emboli or thromboemboli, and the subsequent generation of embolism is an inherently accompanying consequence of CPB, the number of emboli being directly

correlated to the length of the surgical procedure (Heyer et al. page 40, col 2, para 1). Still further, for reasons provided above, transgenic ATIII is construed as product-by-process, and the limitation "preventing a neurological event" broadens the scope of the claims to administration any patient, whether or not they have or are at risk of having "neurological events" or thrombi, etc. Because Berry et al. teach administering to a patient, the patent anticipates the present claims. Because the method steps taught by the reference are identical to the claimed invention, the reference anticipates the invention.

44. Claims 1-23 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Collen (US Patent No. 4,623,718 B1, dated 18 November 1986).

45. Collen teaches the administration of pharmaceutical compositions comprising heparin fragment covalently linked to ATIII for mediating anticoagulative function (abstract, col 1, para 1). The reference also teaches an improved method of treating post-operative thrombosis in patients using the ATIII-heparin conjugate due to its longer half-life in circulation (col 4, para 4). Additionally, the reference demonstrates the antithrombotic effects of the conjugate by administration in rabbits (col 4, para 5). Since neither the instant specification defines a low molecular weight heparin by specific structure, nor the instant claims recite specific molecular weight and/or structure of a low molecular weight heparin, it is inherently implied that low molecular heparin will encompass fragments of the naturally occurring unfractionated heparin.

Furthermore the reference does not explicitly teach neurological events, however, it is well established and evidenced in relevant art that cardiac surgical procedures like CPB can lead to cerebral injury due to emboli formation, resulting in neurological events like stroke, seizures, etc. (Heyer et al. J Card Thor Vasc Anaes 16: 37-42, 2002; page 37, col 1, para 1-2). Additonally, the association of emboli or thromboemboli, and the subsequent generation of embolism is an accompanying consequence of CPB, the number of emboli being directly correlated to the length of the surgical procedure (Heyer et al. page 40, col 2, para 1). Still further, for reasons provided above, transgenic ATIII is construed as product-by-process, and the limitation "preventing a neurological event" broadens the scope of the claims to administration any patient, whether or not they have or are at risk of having "neurological events" or thrombi, etc. Because Collen teaches administering to a patient, the patent anticipates the present claims. Because the method steps taught by the reference are identical to the claimed invention, the reference anticipates the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

46. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

47. Claims 1-5, and 10-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heyer et al. (J Card Thor Vasc Anaes 16: 37-42, 2002), in view of Levy et al. Anaesthesiology 96: 1095-1102, 2002).

48. Heyer et al. teach that emboli is generated during cardiac surgery or CPB, resulting in cerebral injury and neurological events like cognitive dysfunction, stroke or seizures (page 37, col 1, para 1-2). Heyer et al. further demonstrate that administration of heparin to patients reduce the number of emboli resulting from CPB, as well as the occurrence of cognitive dysfunction, when compared to the non-heparin bonded circuits (abstract; Figure 1).

49. Heyer et al. do not teach the administration of ATIII or transgenic ATIII during cardiac surgery.

50. Levy et al. teach that the administration of transgenically produced recombinant human ATIII in patients undergoing cardiac surgery resulted in increased activated clotting times during CPB, thereby reducing thrombotic complications during and after cardiac surgery (abstract; page 1101, col 1, para 3). Although Levy et al. do not explicitly teach neurological events, complications during or after CPB like surgery would inherently encompass neurological complications and events based on prior art teachings.

51. Neither Heyer et al nor Levy et al teach a method for preventing or reducing neurological events associated with emboli due to cardiac surgery in a subject comprising the administration of ATIII and heparin in combination. However, in the absence of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of the references and to administer transgenic ATIII and heparin. Each of the compounds, ATIII and heparin had been taught by the prior art to have antithrombotic or anticoagulative properties during cardiac surgery and to prevent post-operative thrombosis related complications. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process

claims, given the teaching of the prior art of processes using the administration of transgenic ATIII and heparin individually for antithrombotic functions at the time of CPB and subsequently preventing post-surgical coagulative symptoms, that **may** give rise to neurological events in all possibility (based on claim 10 recitation), implicates an usefulness in treating neurological events associated with emboli. It would therefore, have been obvious to administer to a subject both ATIII and heparin, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as antithrombotic compounds for the same purpose in treating neurological events, for example as in the claimed invention. One of ordinary skill in the art would have reasonably expected to obtain the claimed effect of reduction of thrombus (or emboli) generated during cardiac surgery, upon administration of either or both ATIII and heparin since both had been implicated for clinical usefulness in thrombotic disorders in the prior art.

52. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

53. No claims are allowed.

54. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571)

272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

55. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

56. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
8 July 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
July 16, 2009